Amendments to the Specification:

Please replace the paragraph starting at page 14, line 20 of the specification as filed with the following amended paragraph:

To the mixture of fragments (212) is added M adaptors which are capable of being ligated (214) under conventional reaction conditions to the protruding strands of fragments (211) which have an end produced by cleavage with T. Again this results in a population of at least two kinds of fragments (216): those (213) having a Q adaptor at each end ("Q-Q fragments"), and those (215a and 215b) having a Q adaptor at one end and an M adaptor at the other end ("Q-M fragments"). In those instances where there are multiple t restriction sites within the same fragment "M-M fragments" are formed. If this is the case, as illustrated in FIG. 8A by fragment (812), amplification with M and Q primers eliminates M-M fragments from the mixture because of a 1 base pair gap present on one of the strands of the M-M fragments. The length of the M adaptor is selected as described for the Q adaptor; however, the sequence of the M adaptor is selected to be sufficiently different from that of the Q adaptor so that there is little or no possibility of cross-hybridization between primers during an operation such as PCR. M adaptors further have a 3' protruding strand at the end distal to the restriction fragment to which it is ligated, so that such strand is not digested by 3' exonucleases requiring double stranded DNA substrates, such as E. coli exonuclease III.

Please replace the paragraph starting at page 15, line 24 of the specification as filed with the following amended paragraph:

Fragments (228) are then cleaved (232) with S to remove the Q adaptor leaving fragments (230), which are then digested with a 5' 3' exonuclease to produce a population of single stranded fragments (238). Such 5' 3' exonucleases include T7 gene 6 exonuclease (available from United States Biochemical) and may be used in accordance with the protocol of Straus et al. (1991), BioTechniques 10:376-384.

Please replace the paragraph starting at page 16, line 1 of the specification as filed with the following amended paragraph:

As shown in FIG. 2C, fragments (252) from reaction mixture (204) are processed separately as follows: To fragments (252), N adaptors are ligated (254) using conventional protocols to produce a population (256) of fragments having N adaptors at each end. The length of the N adaptor is selected as described for the Q adaptor; however, the sequence of the N adaptor is selected to be sufficiently different from that of the M adaptor and Q adaptor so that there is little or no possibility of cross hybridization during an operation such as PCR. Fragments of population (256) are then cleaved (258) with T, after which the fragments of the mixture are amplified using primers specific for N; thus, the mixture is greatly enriched in fragments lacking a t restriction site. The amplified fragments (260) are then digested (262) with a 3' exonuclease, such as E. coli exonuclease III, to give a mixture (266) of single stranded half length fragments (264).

Please replace the paragraph starting at page 16, line 12 of the specification as filed with the following amended paragraph:

As shown in FIG. 2D, fragments (238) and fragments (266) are combined under conditions that permit complementary strands to hybridize (268). After stable hybrids are formed, repair synthesis (270) is performed on the hybrids to produce double stranded fragments (273), and the double stranded fragments are amplified (272) using primers specific for N (269) and for M (271) to form the reference population of restriction fragments with respect to restriction endonucleases S and T.

Please replace the paragraph starting at page 22, line 16 of the specification as filed with the following amended paragraph:

A preferred method for the use of the reference library is set forth in FIG. 3. Genomic DNA is exacted from individuals of a first (300) and second (302) pool of individuals, designated X

and Y, respectively, in FIG. 3. Preferably, equal amounts of DNA are contributed from each individual. DNA from pool X is cleaved (304) with restriction endonuclease S and B adaptors are ligated to the ends of the resulting fragments. B adaptors are selected as described above for the Q adaptors. Separately, DNA from pool Y is cleaved (306) with restriction endonuclease S and C adaptors are ligated to the ends of the resulting fragments. C adaptors are selected as described above for the Q adaptors. As with the Q adaptors, the B and C adaptors contain primer binding sites for later amplification by PCR. The sequences selected for these primer binding sites should be sufficiently different that there is little or no cross hybridization of the respective primers. Equal amounts of adaptor-fragment complexes from reactions (304) and (306) are combined, after which the complexes are cleaved with restriction endonuclease T, followed by amplification using both B- and C-specific primers in a conventional PCR (308). This gives a population (310) of adaptor-fragment complexes that lack internal t restriction sites. Population (310) is digested (312) with a 3' exonuclease, e.g., E. coli exonuclease III, to give half-length fragments (313), which are then hybridized (314) with fragments (238) to form hybrids (316). Repair synthesis (318) is carried out on hybrids (316), after which the resulting fragments are amplified using primers specific for the primer binding sites of the B, C, and M adaptors.

Please replace the paragraph starting at page 26, line 18 of the specification as filed with the following amended paragraph:

A preferred method of attaching oligonucleotide tags to fragments is further illustrated in FIGS. 5A and 5B. Preferably, fragments are inserted into vector (530) which after insertion comprises the following sequence of elements: first primer binding site (532), restriction site r.sub.1 (534), oligonucleotide tag (536), junction (538), fragment (540), restriction site r.sub.2 (542), and second primer binding site (544). After a sample is taken of the vectors containing tag-fragment conjugates the following steps are implemented: The tag-fragment conjugates are preferably amplified from vector (530) by use of biotinylated primer (548) and labeled primer (546) in a conventional polymerase chain reaction (PCR) in the presence of 5-methyldeoxycytidine triphosphate, after which the resulting amplicon is isolated by

streptavidin capture (556). As used herein, "amplicon" means the product of an amplification reaction. That is, it is a population of polynucleotides, usually double stranded, that are replicated from a few starting sequences. Amplicons may be produced in a polymerase chain reaction or by replication in a cloning vector. To release the captured amplicon from a support with minimal probability of cleavage occurring at a site internal to the fragment of the amplicon, restriction site r.sub.1 preferably corresponds to a rare-cutting restriction endonuclease, such as Pac I, Not I, Fse I, Pme I, Swa I, or the like. Junction (538) which is illustrated as the sequence:

1 5'. . . GGGCCC . . . 3'. . . CCCGGG . . .

causes the DNA polymerase "stripping" reaction to be halted at the G triplet, when an appropriate DNA polymerase is used with dGTP. Briefly, in the "stripping" reaction, the 3' 5' exonuclease activity of a DNA polymerase, preferably T4 DNA polymerase, is used to render the tag of the tag-fragment conjugate single stranded, as taught by Brenner, U.S. Pat. No. 5,604,097; and Kuijper et al. (1992) Gene 112: 147-155 (1992).

Please replace the paragraph starting at page 43, line 3 of the specification as filed with the following amended paragraph:

[0133] Single stranded portions of Sau 3A fragments lacking Taq I sites ~~(Taq fragments)~~ (Taq- fragments) were generated from the plasmid p0T2S with the protocol outlined in FIG. 8B using the adaptors and primers whose sequences are listed below. The Sau 3A digested p0T2S was filled in with dGTP and then an excess of N adaptors were added (852) in a conventional ligation reaction to form product (854), which was then digested with Taq I (856) to give three possible products (858), (860), and (862). Preferably, the 5' ends of the N adaptors are rendered resistant to exonuclease digestion by providing phosphorothioate linkages or other protecting modifications. The reaction mixture was then treated with T7 gene 6 exonuclease (864) to render all fragments single stranded, except those (858) having two N adaptors attached. After treatment with exonuclease I (866) to eliminate single stranded

fragments, N primers were added to the reaction mixture and PCR was carried out (868) to enrich the mixture for fragment (858). The resulting fragments were then treated (860) with exonuclease III to produce the single stranded fragments (862).